(12) UK Patent Application (19) GB (11) 2 148 891 A

(43) Application published 5 Jun 1985

(21) Application No 8426539

(22) Date of filing 19 Oct 1984

(30) Priority data

(31) 58/194358 (32) 19 Oct 1983 (33) JP

(71) Applicant
Nippon Kayaku Kabushiki Kaisha (Japan),
11-2 Fujimi 1-chome, Chiyoda-Ku, Tokyo, Japan

(72) Inventors
Yuya Nakayama,
Kenji Iwata,
Katsutoshi Takahashi

(74) Agent and/or Address for service
J. A. Kemp & Co.,
14 South Square, Gray's Inn, London WC1R 5EU

(51) INT CL[3]
C07C 87/14 A61K 31/13 31/19 C07C 53/16 55/02 59/00

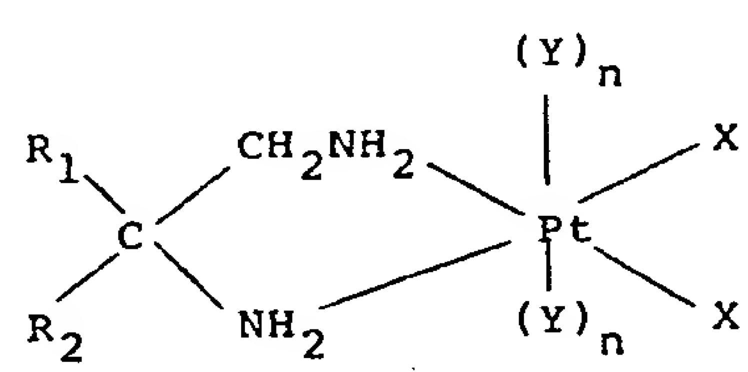
(52) Domestic classification
C2C 1175 20Y 221 225 227 22Y 292 29Y 308 30Y 313 31Y 321 32Y 339 351 355 360 362 366 367 36Y 37X 387 431 434 566 568 606 618 623 625 628 630 638 650 655 65Y 660 771 778 802 80Y AA CQ CT CZ NC NK NW UV
U1S 1313 C2C

(56) Documents cited
GB A 2093845
EP 0055300
EP 0008936
WO 8200145

(58) Field of search
C2C

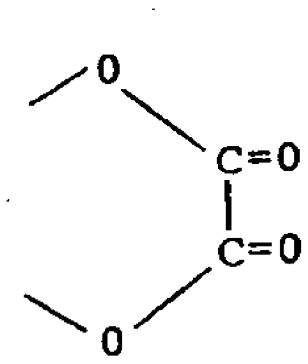
(54) **Platinum-diamine complexes**

(57) Novel complexes of the formula:

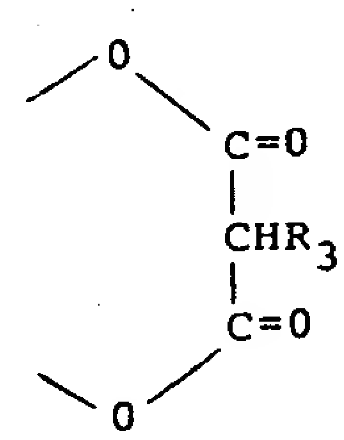


wherein R_1 and R_2, which may be identical or different, each represent an alkyl group of 1 to 3 carbon atoms or jointly represent an alkylene group of 3 to 6 carbon atoms; the two X's, which may be identical or different, each represent a halogen, a $-\mathrm{O}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{CH_3}$ or $-\mathrm{O}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{CH_2Cl}$ group

or jointly represent a



or



group in which R_3 is a lower alkyl group or a $-OM$ group, wherein M is an atom or group which can become a monovalent cation; Y is an $-OH$ group or a halogen; and n is 0 or 1, with the proviso that n is 1 when R_1 and R_2 jointly represent an alkylene group of 5 carbon atoms, and X is chlorine, have antitumour activity and a lower renal toxicity than *cis*-Platin now widely used as a carcinostatic in clinical medicine.

GB 2 148 891 A

SPECIFICATION

Novel platinum complexes

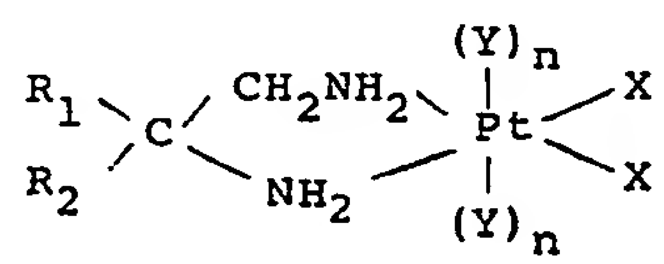
Background of the invention

It has already been known that certain platinum complexes have a carcinostatic effect [e.g., Journal of Pharmaceutical Sciences, Vol. 65, No. 3, 315-328 (1976) and Journal of Inorganic Biochemistry, 11, 139-149 (1979)].

Among these compounds, cis-dichlorodiammineplatinum (cis-Platin, generic name) has a very excellent carcinostatic effect and is now widely used as clinical medicine. However, this compound is disadvantageous in that it is high in toxicity, particularly in renal toxicity and is very low in water-solubility.

Summary of the invention

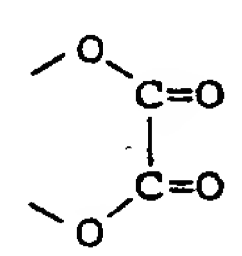
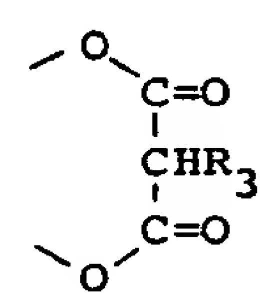
Accordingly, the present inventors have conducted extensive research and have consequently found that a plantinum-diamine complex represented by the general formula (I):



(I)

wherein R_1 and R_2 each represents lower alkyl group having 1 to 3 carbon atoms or jointly represent an alkylene group having 3 to 6 carbon atoms; two X's each represents a halogen atom,

$$-O-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-CH_3 \quad \text{or} \quad -O\underset{\underset{O}{\|}}{C}CH_2Cl$$

or jointly represent a group represented by  or 

in which R_3 is a lower alkyl group or a group represented by $-OM$ (wherein M is an atom which can become a monovalent cation); Y is $-OH$ or a halogen atom; and n is 0 or 1, and n is 1 when R_1 and R_2 jointly represent an alkylene group having 5 carbon atoms and X is chlorine, has an excellent antitumor effect and at the same time has a lower renal toxicity and a higher water-solubility than cis-Platin. This invention has been accomplished on the basis of this finding.

The object of this invention is to provide a novel platinum-diamine complex having an antitumor activity and a low renal toxicity and a process for producing the same.

Detailed description of the invention

In the compound represented by the above general formula (I), the lower alkyl group having 1 to 3 carbon atoms for R_1 and R_2 include methyl group, ethyl group, n-propyl group and isopropyl group. The alkylene group having 3 to 6 carbon atoms formed by combination of R_1 and R_2 includes trimethylene group, tetramethylene group, pentamethylene group and hexamethylene group. The lower alkyl group for R_3 includes methyl group, ethyl group, etc. M in R_3 includes hydrogen, monovalent metals such as sodium, potassium and the like, ammonia, etc. The halogen includes chlorine, bromine, iodine and fluorine.

Among the compounds represented by the above general formula (I), typical ones are listed below.

1. cis-Dichloro-1,2-diamino-2-methylpropane platinum.
2. cis-Dichloro-trans-dihydroxy-1,2-diamino-2-methylpropane platinum.
3. cis-Tetrachloro-1,2-diamino-2-methylpropane platinum.
4. cis-Dichloro-1,2-diamino-2-methylbutane platinum.
5. cis-Dichloro-1,2-diamino-2-ethylbutane platinum
6. cis-Oxalato-1,2-diamino-2-ethylbutane platinum.
7. cis-Dichloro-trans-dihydroxy-1,2-diamino-2-ethylbutane platinum.
8. cis-Tetrachloro-1,2-diamino-2-ethylbutane platinum.
9. cis-2-Ethylmalonato-1,2-diamino-2-ethylbutane platinum.
10. cis-2-Hydroxymalonato-1,2-diamino-2-ethylbutane platinum.
11. cis-Dichloro-trans-dihydroxy-1-amino-1-aminomethylcyclohexane platinum.
12. cis-Tetrachloro-1-amino-1-aminomethylcyclohexane platinum.

13. cis-Oxalato-1-amino-1-aminomethylcyclohexane platinum.
14. Sodium salt of cis-2-hydroxymalonato-1-amino-1-aminomethylcyclohexane platinum.
15. cis-bis(Chloroacetato)-1-amino-1-aminomethylcyclohexane platinum.
16. cis-bis(Pyruvato)-1-amino-1-aminomethylcyclohexane platinum.
17. cis-2-Ethylmalonato-1-amino-1-aminomethyl cyclohexane platinum.
18. cis-Dichloro-1-amino-1-aminomethylcylopentane platinum.
19. cis-Dichloro-trans-dihydroxy-1-amino-1-aminomethylcyclopentane platinum.
20. cis-Tetrachloro-1-amino-1-aminomethyl cyclopentane platinum.
21. cis-Oxalato-1-amino-1-aminomethylcyclopentane platinum.
22. cis-2-Ethylmalonato-1-amino-1-aminomethylcyclopentane platinum.
23. cis-2-Hydroxymalonato-1-amino-1-aminomethycyclopentane platinum.

Physicochemical properties of these compounds are shown in Table 1.

TABLE 1

No.	*Appearance*	*Melting point (°C)*	*Solubility in water (mg/ml)*	*1) TLC Rf*	*Molecular formula*	*Elementary analysis*	*Calcd. %*	*Found %*	*IR absorption spectrum (cm⁻¹)*
1	Yellow crystals	280-285° (decomp.)	5	0.49	$C_4H_{12}N_2Cl_2Pt$	C	13.57	13.30	3290, 3225, 3125, 2980, 1590, 1580, 1474, 1460, 1400, 1380, 1344, 1304, 1268, 1218, 1190, 1140, 1122, 1010, 968, 802, 720
						H	3.42	3.65	
						N	7.91	7.80	
						Cl	20.02	19.68	
2	Light-yellow crystals	279-281° (decomp.)	>20	0.56	$C_4H_{14}N_2O_2Cl_2Pt$	C	12.38	12.25	3570, 3500, 3245, 2900, 2625, 2550, 2475, 2090, 1618, 1568, 1494, 1380, 1358, 1314, 1302, 1212, 1182, 1136, 1060, 1010, 980, 900, 808, 738
						H	3.64	3.76	
						N	7.22	7.15	
						Cl	18.27	18.04	
3	Yellow crystals	264-265° (decomp.)	>12	0.51	$C_4H_{12}N_2Cl_4Pt$	C	11.30	11.45	3475, 3250, 3200, 3100, 2990, 1575, 1560, 1474, 1410, 1340, 1304, 1220, 1200, 1140, 1100, 1020, 980, 888, 820, 760, 720
						H	2.85	2.98	
						N	6.59	6.57	
						Cl	33.36	32.48	
4	Yellowish-white crystals	271° (decomp.)	3.5	0.70	$C_5H_{14}N_2Cl_2Pt$	C	16.31	16.41	3460, 3250, 3200, 3130, 2980, 2900, 1580, 1465, 1400, 1195, 1130, 800
						H	3.83	3.90	
						N	7.61	7.58	
						Cl	19.26	19.40	

TABLE 1 (Continued)

No.	Appearance	Melting point (°C)	Solubility in water (mg/ml)	1) TLC Rf	Molecular formula	Elementary analysis	Calcd. %	Found %	IR absorption spectrum (cm^{-1})
5	Yellow crystals	281° (decomp.)	>2.5	0.63	$C_6H_{16}N_2Cl_2Pt$	C H N Cl	18.86 4.22 7.33 18.55	18.71 4.02 7.15 18.63	3500, 3245, 3200, 2975, 2890, 1590, 1465, 1390, 1195, 1130, 795, 700
6	White crystals	>300°	>5	0.58	$C_8H_{16}N_2O_4Pt$	C H N	24.06 4.04 7.02	24.28 4.15 6.90	3450, 3230, 3160, 2985, 2900, 1708, 1687, 1665, 1575, 1465, 1380, 1255, 1235, 1140, 1000, 803
7	Light-yellow crystals	221° (decomp.)	13	0.78	$C_6H_{18}N_2O_2Cl_2Pt$	C H N Cl	17.31 4.36 6.73 17.03	17.48 4.41 6.88 17.53	3500, 3470, 3190, 2980, 2885, 2440, 1580, 1470, 1400, 1300, 1260, 1140, 1045
8	Yellow crystals	251° (decomp.)	5	0.75	$C_6H_{16}N_2Cl_4Pt$	C H N Cl	15.90 3.56 6.18 31.30	16.12 3.60 6.37 31.15	3600, 3450, 3250, 3175, 3100, 2975, 2880, 1635, 1575, 1560, 1465, 1450, 1200, 1130, 1020, 880
9	White crystals	230° (decomp.)	25	0.86	$C_{11}H_{22}N_2O_4Pt$	C H N	29.93 5.02 6.35	29.90 5.22 6.41	3450, 3220, 3110, 2980, 2880, 1660 1620, 1465, 1375, 1400, 1295, 1235
10	White crystals	248° (decomp.)	16	0.62	$C_9H_{18}N_2O_5Pt$	C H N	25.18 4.23 6.53	25.15 4.44 6.69	3460, 3180, 3100, 2980, 2840, 1680, 1635, 1465, 1420, 1370, 1300, 1250, 1195, 1130, 930 760

TABLE 1 (Continued)

No.	Appearance	Melting point (°C)	Solubility in water (mg/ml)	1) TLC Rf	Molecular formula	Elementary analysis	Calcd. %	Found %	IR absorption spectrum (cm^{-1})
11	Light yellow crystals	217° (decomp.)	>2	0.78	$C_7H_{18}N_2O_2Cl_2Pt$	C H N Cl	19.63 4.24 6.54 16.54	19.82 4.14 6.11 16.22	3550, 3530, 3200, 3190, 2950, 2875, 1575, 1560, 1460, 1450, 1275, 1180, 1080, 1015, 850, 715
12	Yellow crystals	254-255° (decomp.)	>15	0.80	$C_7H_{16}N_2Cl_4Pt$	C H N Cl	18.08 3.47 6.02 30.49	18.27 3.42 6.15 30.59	3460, 3280, 3160, 3075, 2980, 2860, 1575, 1545, 1460, 1450, 1210
13	White crystals	>300°	>2.5	0.67	$C_9H_{16}N_2O_4Pt$	C H N	26.28 3.92 6.81	26.03 3.82 6.75	3440, 3210, 3140, 2935, 2860, 1705, 1685, 1660, 1595, 1570, 1460, 1380, 1250, 1148, 997, 805
14	White powder	225°	Readily soluble	0.59	$C_{10}H_{17}N_2O_5Na$ $Pt.3H_2O$	C H N	23.22 4.48 5.42	22.96 3.60 5.23	3440, 3170, 3100, 2930, 2875, 1665, 1685, 1465, 1370, 1230, 1175, 1080, 950, 738
15	White crystals	170-173°	>1.5	0.90	$C_{11}H_{20}N_2O_4Cl_2$ Pt	C H N	24.10 4.05 5.62	24.38 4.11 5.32	3450, 3220, 3150, 2940, 2865, 1708, 1685, 1660, 1660, 1600, 1563, 1460, 1380, 1250, 1150, 805

TABLE 1 (Continued)

No.	Appearance	Melting point (°C)	Solubility in water (mg/ml)	1) TLC Rf	Molecular formula	Elementary analysis	Calcd. %	Found %	IR absorption spectrum (cm^{-1})
16	White crystals	263° (decomp.)	>2	0.73	$C_{13}H_{22}N_2O_6Pt$	C H N	31.39 4.46 5.63	31.79 4.39 5.33	3450, 3210, 3110, 2930, 2860, 1630, 1705, 1630, 1590, 1450, 1380, 1210, 1140, 1070, 800, 700
17	White crystals	265° (decomp.)	8	0.84	$C_{12}H_{22}N_2O_4Pt$	C H N	31.79 4.89 6.18	31.85 4.82 6.32	3430, 3200, 3100, 2940, 2870, 1630, 1450, 1370, 1340, 1300, 1230, 795
18	Yellow crystals	279° (decomp.)	>3	0.63	$C_6H_{14}N_2Cl_2Pt$	C H N Cl	18.96 3.71 7.37 18.65	18.80 3.81 7.19 18.41	3470, 3240, 3180, 3110, 2950, 2870, 1580, 1450, 1200, 1185, 1135, 1020, 950, 795
19	Light-yellow crystals	212° (decomp.)	>10	0.75	$C_6H_{16}N_2O_2Cl_2Pt$	C H N Cl	18.86 4.22 7.33 18.55	18.97 4.38 7.01 18.35	3520, 3170, 3080, 2940, 2875, 1590, 1560, 1455, 1320, 1210, 1060, 1030
20	Yellow crystals	>300° Changed to yellow at about 260°C	18	0.75	$C_6H_{14}N_2Cl_4Pt$	C H N Cl	15.98 3.13 6.21 31.44	16.18 3.21 6.09 31.15	3425, 3250, 3200, 3110, 2970, 2880, 1555, 1455, 1395, 1185, 1150, 1110

TABLE 1 (Continued)

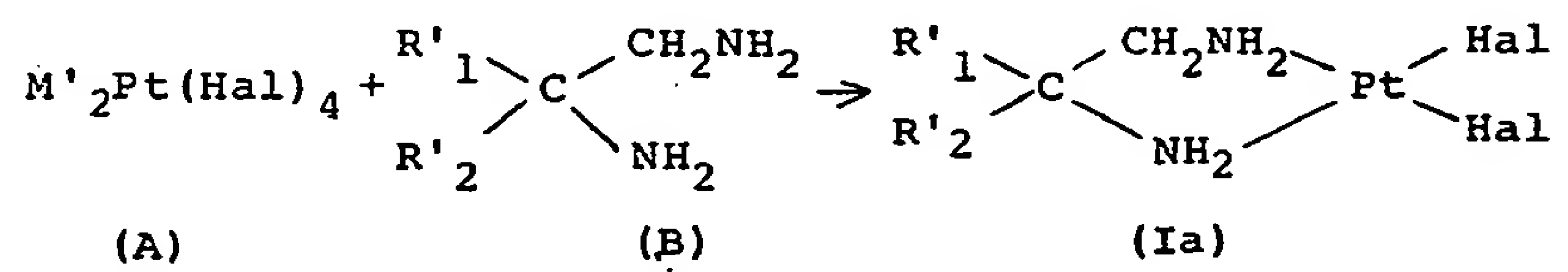
No.	Appearance	Melting point (°C)	Solubility in water (mg/ml)	1) TLC Rf	Molecular formula	Elementary analysis	Calcd. %	Found %	IR absorption spectrum (cm⁻¹)
21	White crystals	>300°	>11	0.58	$C_8H_{14}N_2O_4Pt$	C	24.19	24.01	3400, 3215, 3130, 2960, 2880, 1695, 1672, 1450, 1393, 1300, 1250, 1210, 1160, 1030, 898, 805
						H	3.55	3.67	
						N	7.05	7.21	
22	White crystals	239° (decomp.)	>50	0.80	$C_{11}H_{20}N_2O_4Pt$	C	30.07	30.25	3460, 3210, 3110, 2975, 2880, 1640, 1450, 1380, 1235, 800
						H	4.59	4.81	
						N	6.38	6.16	
23	White crystals	250° (decomp.)	5	0.55	$C_9H_{16}N_2O_5Pt$	C	25.30	25.37	3500, 3200, 3110, 2960, 2880, 1695, 1660, 1460, 1405, 1335, 1240, 1160, 1120, 760
						H	3.77	3.88	
						N	6.56	6.77	

1) adsorption plate: Avicel SF; Developer: BuOH, AcOH, H_2O (5:2:3)

As is evident from the above table, the compounds of this invention are relatively rich in water-solubility and hence are suitable for injections and the like.

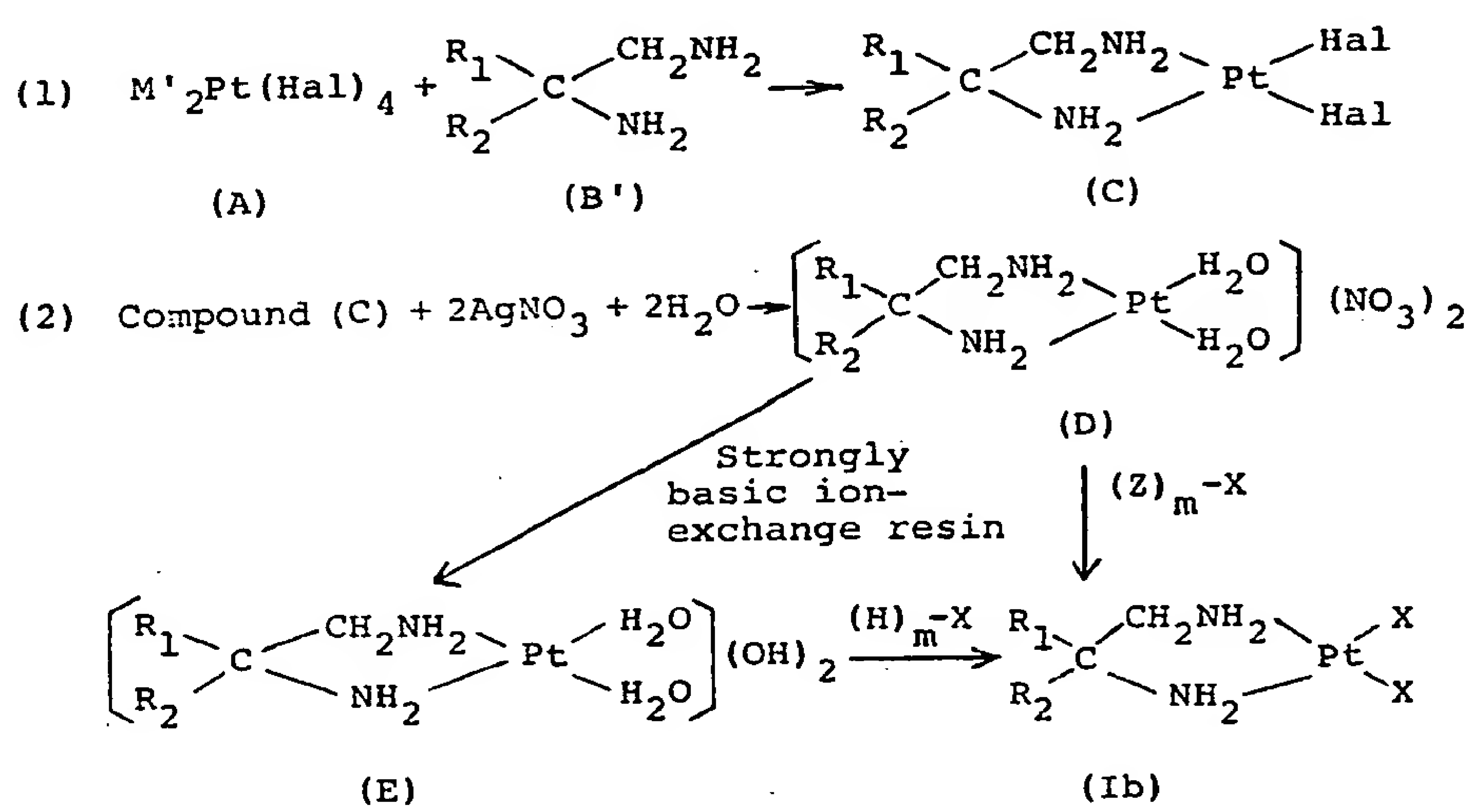
The compounds of this invention can be produced by any of the following processes (a) to (c).

Process (a):



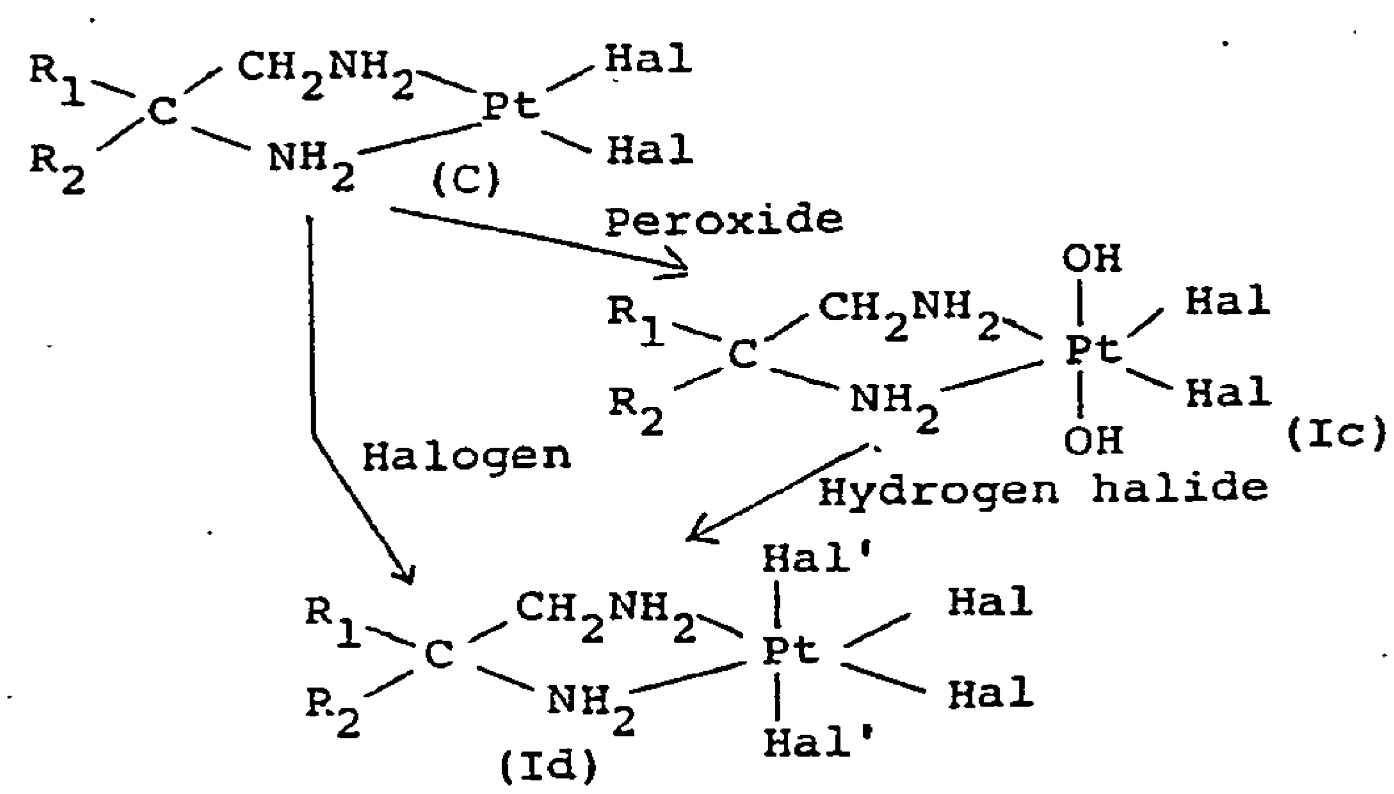
wherein R'_1 and R'_2 each represents a lower alkyl group having 1 to 3 carbon atoms or jointly represent an alkylene group having 3 to 6 carbon atoms; M' is an alkali metal; and Hal is a halogen atom, and Hal is a halogen atom except chlorine when R'_1 and R'_2 jointly represent an alkylene group having 5 carbon atoms.

Process (b):



wherein R_1, R_2, M' and X are as defined above, Hal is a halogen atom, Z is an atom or a molecule which can become a monovalent or divalent cation, and m is 1 or 2, when X is a halogen atom, Z is an atom or a molecule other than a hydrogen atom, and when R_1 and R_2 form jointly an alkylene group having 5 carbon atoms, X is a group other than chlorine.

Process (c):



wherein R_1 and R_2 are as defined above, and Hal and Hal' are the same or different halogen atoms.

The process (a) is suitable for obtaining a compound of the general formula (Ia), i.e., a compound of the general formula (I) in which X is a halogen atom and n is is 0. That is to say, by reacting a halogenated platinate (II) of the general formula (A) with a diamine of the general formula (B), there can be obtained a halogenodiammineplatinum of the general formula (Ia), i.e., a compound of the general formula (I) in which

R_1 and R_2 each represents a lower alkyl group having 1 to 3 carbon atoms or jointly represent an alkyl group having 3 to 6 carbon atoms; X is a halogen atom and X is a halogen atom except chlorine when R_1 and R_2 jointly represent an alkylene group having 5 carbon atoms, and n is 0.

The halogenated platinate (II) includes, for example, alkalimetal salts of chlorinated platinic (II) acid, brominated platinic (II) acid, iodinated plantinic (II) acid and fluorinated platinic (II) acid. Among them, potassium halogenoplatinates (II) such as potassium tetrachloroplatinate (II), potassium tetraiodoplatinate (II) and the like are preferred.

The diamine of the general formula (B) includes, for example, those in which each of R_1 and R_2 is an alkyl group having 1 to 3 carbon atoms, for example, 1,2-diamino-2-methylpropane, 1,2-diamino-2-methylbutane, 1,2-diamino-2-ethylbutane, 1,2-diamino-2-methylpentane, 1,2-diamino-2,3-dimethylbutane, 1,2-diamino-2-isopropyl-3-methylbutane and the like, 1-amino-1-aminomethylcyclopentane, etc.

The amount of the diamine to be used is 0.5 to 10 equivalents, preferably 1 to 1.2 equivalents to an equivalent of the halogenated platinic (II) acid or salt thereof. The reaction temperature is 0° to 100°C, preferably 20° to 60°C, and as the reaction time, 5 minutes to 2 hours is needed.

The process (b) can be employed for producing the compound in which n is 0 in general formula (I). That is to say, a diammineplatinum of the general formula (Ib), i.e., a compound of the general formula (I) in which n is 0, can be obtained by reacting the compound (A) with the compound (B′) in the same manner as in the above-mentioned process (a) to obtain the compound (C), treating the resulting compound (C) with silver nitrate in an aqueous solution to obtain a solution of aquo complex of the general formula (D), optionally treating the solution of aquo complex with a strongly basic ion-exchange resin to obtain a solution of aquo complex of the general formula (E), and then reacting these aquo complexes with a compound of the general formula:

$$(Z)_m-X$$

wherein Z, m and x are as defined above. When the solution of aquo complex is treated with a strongly basic ion-exchange resin, (for example, Dowex 1-8X), the resulting solution is reacted with an acid of the formula of $(H)_m-X$, in which m and X are as defined above.

As the halogenated platinate (II) of the general formula (A), there are exemplified the same compounds as exemplified in the case of the above-mentioned process (a), and there are preferably exemplified potassium tetrachloroplatinate (II), potassium tetraiodoplatinate (II), etc.

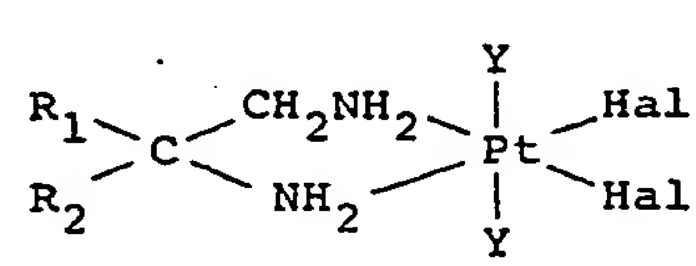
As the amine of the general formula (B′), there are exemplified 1-amino-1-aminomethylcyclobutane, 1-amino-1-aminomethylcyclohexane, 1-amino-1-aminomethylcycloheptane and the like in addition to the same compounds exemplified in the case of the process (a).

The amounts of the compounds of the general formulas (A) and (B) to be used and the reaction conditions are the same as in the process (a).

Next, it is sufficient that the reaction of the compound (C) with silver nitrate is carried out at 0° to 100°C, preferably 20° to 70°C for 10 minutes to 24 hours. The amount of silver nitrate to be used is one equivalent or less, preferably 0.7 to 1 equivalent, more preferably 0.95 to 0.99 equivalent to an equivalent of the compound of the general formula (C).

The compound of the above general formula $(Z)_m-X$ includes, for example, pyruvic acid, chloroacetic acid, methylmalonic acid, ethylmalonic acid, propylmalonic acid, butylmalonic acid, hydroxymalonic acid, oxalic acid, their sodium salts, potassium salts and ammonium salts, and sodium chloride, potassium chloride, etc. The amount of these compounds to be used is one equivalent or more, preferably 1 to 10 equivalents, more preferably 1 to 1.2 equivalents to an equivalent of the compound (A). The reaction temperature is 0° to 100°C, preferably 20° to 60°C, and as the reaction time, 10 minutes to 2 hours is needed.

The process (c) is suitable for obtaining a compound of the general formula:



i.e., a compound of the general formula (I) in which X is a halogen atom and n is 1. That is to say, a transdihydroxy derivative of the formula (Ic) corresponding to the formula (I) in which Y is OH can be obtained by reacting a halogenodiammineplatinum of the general formula (C) obtained by the above-mentioned process (a) or (b) with a peroxide.

Further, a trans-dihalo derivative of the formula (Id) corresponding to the formula (I) in which Y is a halogen atom can be obtained by treating the compound of the formula (Ic) with hydrogen halide, or by reacting the compound of the general formula (C) with halogen.

The peroxide includes, for example, hydrogen peroxide, etc. The amount of the peroxide to be used is 2 to 50 equivalents, preferably 5 to 10 equivalents to an equivalent of the compound (C). The reaction temperature is 0° to 100°C, preferably 20° to 90°C, and as the reaction time, 30 minutes to 2 hours is needed.

As the hydrogen halide, there are exemplified hydrogen chloride, hydrogen bromide, hydrogen fluoride

and hydrogen iodide, among which hydrogen chloride is preferred. The amount thereof to be used is one equivalent or more, preferably 1 to 10 equivalents, more preferably 1 to 5 equivalents to an equivalent of the compound (Ic). The reaction temperature is 0° to 100°C, preferably 20° to 90°C, and as the reaction time, 10 minutes to 2 hours is needed.

As halogen, there are exemplified, for example, fluorine, chlorine and bromine, among which chlorine is preferred. The amount thereof to be used is 1 to 100 equivalents, preferably 10 to 50 equivalents to an equivalent of the compound (C). The reaction temperature is adequately 50° to 80°C and the reaction time is 1 to 2 hours.

In the above-mentioned processes (a) to (c), water is usually used as a solvent, and if necessary, these processes are carried out while shielding the light. The crude crystals or crude powder obtained is, if necessary, purified by recrystallization or reprecipitation from hydrochloric acid, water, a water-ethanol mixed solution of the like.

Next, the antitumor effect and acute toxicity of typical compounds of this invention are explained referring to Experimental Example.

Experimental Example

(1) Test for inhibitory activity on multiplication of mouse leukemia L-1210 initially cultured cells

Mouse leukemia L-1210 cells collected from the abdominal cavities of DBA/2 mouse were incubated in a 5% CO_2 incubator at 37°C for 48 hours by using a RPMI 1640 medium containing 10% of bovine fetal serum and 5 μM of 2-mercaptoethanol. Inbibition percentage (%) of multiplication was calculated from the numbers of cells in the case of addition and no addition of each drug, and IC_{50} value (a concentration at which multiplication was inhibited by 50%) was obtained from a graph prepared by plloting a drug concentration and the inhibition percentage on a logarithmic probability paper. The results obtained are shown in Table 2.

TABLE 2

Compound No.	*IC_{50} (mcg/ml)*
13	0.021
18	0.02
19	0.60

(2) Test for antitumor activity on mouse leukemia L-1210.

Into 6-weeks-old female CDF_1 mouse were inoculated 1×10^5 L-1210 cells, and each drug was administered intraperitoneally once a day for 5 consecutive days, starting 24 hours after the inoculation. Physiological saline was administered to a control group. From the average survival periods of the drug-treated group and the control group (abbreviated as T and C, respectively), T/C percentage (T/C × 100) was determined.

(3) Acute toxicity test

Each compound of this invention was intraperitoneally administered 5 times to mouse having L-1210 cancer, and its median letal dose (LD_{50}) was determined.

The results of above (2) and (3) are shown in Table 3.

TABLE 3

Compound No.	*Antitumor effect shown by T/C percentage (dose, mg/kg)*								*LD_{50}*
	(0.5)	*(1)*	*(2)*	*(4)*	*(8)*	*(16)*	*(32)*	*(64)*	
1		133	171	206	124	51			5.5
3		127	139	162	154	60			7.5
5	135	181	291	199	82				3.0
6		130	152	226	206	211			16.8
11				162	237	275	108	67	14.0
12	137	200	259	224	95				3.5
13	146	188	296	230	218				7.2
15	135	175	200	299	130				6.0
18	179	226	344	141	92				3.0
19				138	174	323	113	80	24.0
21	124	141	161	189	166				7.6

As is evident from Table 3, the compounds of this invention have a high inhibitory effect on growth of mouse leukemia (L-1210) cells and an excellent life prolongation effect on mouse inoculated with L-1210 cells.

(4) Renal toxity test

Each drug was intraperitoneally administrered once to 6-weeks-old CDF_1 mouse. Ninety-six hours after the administration, the blood is collected and the blood urea nitrogen concentration (BUN) was determined.

The results are shown in Table 4.

TABLE 4

Compound No.	*Dose (mg/kg)*	*Weight ratio**	*BUN (mg/dl)*
Physiological saline	-	1.05	22.7
cis-Platin	22.6	0.76	136.6
1	18.0	0.88	19.3
3	27.0	0.84	18.6
5	30.4	0.73	25.1
11	144.0	0.72	21.9
12	36.0	0.72	18.0
13	20.3	0.76	16.5
15	35.6	0.75	17.2
18	30.4	0.77	16.5
19	108.0	0.91	18.8
21	45.0	0.89	25.3

* Ratio of the body weight on the drug administration day to the body weight at 96 hours after the administration.

As is evident from Table 4, the compounds of this invention bring about a greatly lowered BUN value which is one-fifth or less as much as that brought about by commercially available cis-Platin, and substantially equal to or smaller than that brought about by physiological saline, and it can be seen that said compounds are very low in renal toxicity.

The compound of this invention is, therefore, expected as an antitumor agent having a very low renal toxicity. When used as an antitumor agent, the compound of this invention is intravenously administered usually in the form of an injection, and its dosage is about 1 to 80 mg/m^2 (surface area of human body) a time.

The process for producing the compound of this invention is explained below with reference to Examples.

Example 1

cis-Dichloro-1,2-diamino-2-methylpropane platinum (compound No. 1).

In 3.5 ml of water was dissolved 207.6 mg of potassium tetrachloroplatinate (II), and a solution of 45 mg of 1,2-diamino-2-methylpropane dissolved in 1.5 ml of water was added dropwise with stirring. The resulting mixture was subjected to reaction at room temperature for 1.5 hours and then cooled for 4 days, and the crystals deposited was collected by filtration, washed with water, and then dried to obtain 126 mg of crude crystals of compound No. 1. The crude crystals were recrystalized from 4.5 ml of hot water to obtain 50.9 mg of compound No. 1 in a pure form.

Example 2

cis-Dichloro-1,2-diamino-2-ethylbutane platinum (compound No. 5).

In 20 ml of water was dissolved 2.08 g of potassium tetrachloroplatinate (II), after which a solution of 3.42 g of potassium iodide dissolved in 5 ml of water was added dropwise, and the resulting mixture was subjected to reaction with stirring at 40°C for 10 minutes to obtain a black solution of potassium tetraiodoplatinate (II). A solution of 638 mg of 1,2-diamino-2-ethybutane dissolved in 15 ml of water was added dropwise to the

black solution, and the resulting mixture was stirred at room temperature for 2 hours. The deposited precipitate was collected by filtration, washed with water, and then dried to obtain 2.77 g of yellowish-brown powder of cis-diiodo-1,2-diamino-2-ethylbutane platinum. In 22.5 ml of water was suspended 2.77 g of the resulting diiods compound, and 1.64 g of silver nitrate was added, after which the resulting mixture was subjected to reaction with stirring at 65°C for 10 minutes and then at room temperature for 1 hour and thereafter filtered, and the silver iodide on the filter was washed with water.

The filtrate and the washings were combined, and 0.795 g of potassium chloride was added with stirring, after which the resulting mixture was allowed to stand at 40°C for 10 minutes and then in a cold place for 2 hours, and the deposited crystals were collected by filtration, washed with water, and then dried to obtain 1.36 g of crude crystals of compound No. 5.

The crude crystals were recrystallized from 110 ml of 0.1 N hydrochloric acid to obtain 1.10 g of compound No. 5 in a pure form.

Example 3

cis-Dichloro-1-amino-1-aminomethylcyclopentane platinum (compound No. 18).

Reaction was conducted in the same manner as in Example 2, except that 793 mg of 1-amino-1-aminomethylcyclopentane was used in place of 1,2-diamino-2-ethylbutane, to obtain 1.38 g of crude crystals of compound No. 18. The crude crystals were recrystallized from 110 ml of 0.1 N hydrochloric acid to obtain 930 mg of compound No. 18 in a pure form.

Example 4

cis-Dichloro-trans-dihydroxy-1,2-diamino-2-methylpropane platinum (compound No. 2).

In 5 ml of water was suspended 1 g of compound No. 1, after which 3.6 ml of a 30% aqueous hydrogen peroxide solution was added dropwise with stirring, and the resulting solution was subjected to reaction at room temperature for 2 hours. The reaction solution was ice-cooled for 1 hour, and the deposited solid was collected by filtration, washed with water, and then dried to obtain 605.4 mg of crude crystals of compound No. 2. The crude crystals were dissolved in 24 ml of hot water, and 75 ml of acetone was added, after which the resulting mixture was ice-cooled, and after two hours, the precipitate was collected by filtration and then dried to obtain 542.7 mg of compound No. 2 in a pure form.

Example 5

cis-Dichloro-trans-dihydroxy-1-amino-1-aminomethylcyclohexane platinum (compound No. 11).

(1) Reaction was conducted in the same manner as in Example 2, except that 1.41 g of 1-amino-1-aminomethylcyclohexane was used in place of 1,2-diamino-2-ethylbutane, to obtain 1.59 g of crude crystals of cis-dichloro-1-amino-1-aminomethycyclohexane platinum. The crude crystals were dissolved in 10 ml of dimethylformamide, and the resulting solution was filtered. Thereafter, 40 ml of methanol was added to the filtrate and the resulting mixture was ice-cooled, after which the precipitate was collected by filtration, washed with methanol, and then dried to obtain 1.34 g of the product in a pure form.

(2) Reaction was conducted in the same manner as in Example 4, except that 1 g of the platinum complex obtained in (1) was used in place of the compound No. 1 in Example 4, to obtain 640 mg of compound No. 11 in a pure form.

Example 6

cis-Dichloro-trans-dihydroxy-1-amino-1-aminomethylcyclopentane platinum (compound No. 19).

Reaction was conducted in the same manner as in Example 4, except that 1.0 g of compound No. 18 was used in place of compound No. 1, to obtain 537 mg of compound No. 19.

Example 7

cis-Tetrachloro-1,2-diamino-2-methylpropane platinum (compound No. 3).

In 14.3 ml of 0.2 N hydrochloric acid, 489 g of compound No. 2 was stirred at 80°C for 30 minutes. The reaction solution was concentrated to a volume of 2.5 ml, after which the concentrate was ice-cooled for 1 hour, and the precipitate was collected by filtration, washed with water, and then dried. There was obtained 437.1 mg of crude crystals of compound No. 3. The crude crystals were recrystallized from 5 ml of 0.1 N hydrochloric acid to obtain 169.3 mg of compound No. 3 in a pure form.

Example 8

cis-Tetrachloro-1-amino-1-aminomethylcyclohexane platinum (compound No. 12).

In 0.5 ml of water was suspended 100 mg of compound No. 11, after which 0.2 ml of 36% hydrochloric acid was added dropwise, and the reaction solution was stirred at 70° to 75°C for 15 minutes. It was then ice-cooled and the precipitate was collected by filtration, washed with water, and then dried to obtain 79 mg of compound No. 12 in a pure form.

Example 9

cis-Oxalato-1-amino-1-aminomethylcyclohexane platinum (compound No. 13).

A mixture of 39.4 mg of the platinum complex obtained by the process of Example 5-(1), 333 mg of silver nitrate and 10 ml of water was stirred at room temperature for 4 hours, after which the reaction mixture was filtered and the residue was washed with water. The filtrate and the washings were combined, followed by adding thereto a solution prepared by dissolving 1.51 mg of oxalic acid dihydrate dissolved in 2 ml of water and neutralizing the resulting solution to about pH6 with a 30% aqueous sodium hydroxide solution. The resulting mixture was stirred at room temperature for 3 hours and then at 60° to 65°C for 1 hour. This mixture was ice-cooled and the precipitate was collected by filtration, washed with water, and then dried to obtain 295 mg of light-gray crystals of compound No. 13. The crystals were dissolved in 150 ml of methanol with heating and the resulting solution was treated with active carbon, after which most of the methanol was distilled off, and the residue was cooled, separated by filtration, washed with methanol, and then dried to obtain 239 mg of white crystals of compound No. 13.

Example 10

cis-Oxalato-1-amino-1-aminomethylcyclopentane platinum (compound No. 21).

Reaction was conducted in the same manner as in Example 9, except that compound No. 18 was used in place of the platinum complex obtained in Example 5-(1), to obtain 213 mg of light-gray crystals of compound No. 21. The crystals were dissolved in 64 ml of methanol with heating and then treated in the same manner as in Example 9 to obtain 182 mg of white crystals of compound No. 21.

Example 11

cis-Oxalato-1,2-diamino-2-ethylbutane platinum (compound No. 6).

Reaction was conducted in the same manner as in Example 9, except that 382 mg of compound No. 5 was used in place of the platinum complex obtained in Example 5-(1), to obtain 270 mg of gray crystals of compound No. 6. The crystals were dissolved in 81 ml of methanol with heating and then treated in the same manner as in Example 9 to obtain 180 mg of white crystals.

Example 12

cis-Dichloro-1,2-diamino-2-methylbutane platinum (compound No. 4).

Reaction was conducted in the same manner as in Example 2, except that 1,2-diamino-2-methylbutane was used in place of 1,2-diamino-2-ethylbutane, to obtain 1.44 g of crude crystals of compound No. 4. The crude cyrstals were recrystallized from 60 ml of 0.1 N hydrochloric acid to obtain 780 mg of pure crystals.

Example 13

cis-Dichloro-trans-dihydroxy-1,2-diamino-2-ethylbutane platinum (compound No. 7).

Reaction was conducted in the same manner as in Example 4, except that compound No. 5 was used in place of compound No. 1, to obtain 512 mg of crystals of compound No. 7.

Example 14

cis-Tetrachloro-1,2-diamino-2-ethylbutane platinum (compound No. 8).

In 4 ml of water was suspended 832 mg of compound No. 7 obtained by the process of Example 13, after which 1.7 ml of 35% hydrochloric acid was added, and the resulting mixture was stirred at 80°C for 30 minutes. After being ice-cooled, the mixture was filtered, and the residue was washed with water, and then dried to obtain 818 mg of crystals of compound No. 8.

Example 15

cis-Tetrachloro-1-amino-1-aminomethylcyclopentane platinum (compound No. 20).

Reaction was conducted in the same manner as in Example 13, except that compound No. 19 was used in place of compound No. 7. The reaction solution was allowed to stand for 3 days to deposit yellow crystals. The formed crystals were collected by filtration, washed with water, and then dried to obtain 582 mg of crystals of compound No. 20.

Example 16

Sodium salt of cis-2-hydroxymalonato-1-amino-1-aminomethylcyclohexane platinum (compound No. 14).

In 3 ml of water was suspended 349 mg of the platinum complex obtained in Example 5-(1), after which 333 mg of silver nitrate was added, and the resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was filtered and the residue was washed with water. The filtrate and the washings were combined, followed by adding thereto a solution prepared by dissolving 144 mg of 2-hydroxymalonic acid in 1 ml of water and neutralizing the resulting solution to pH6 with 30% aqueous sodium hydroxide solution. The resulting mixture was stirred at room temperature for 1 hour and then at 50° to 60°C for 30 minutes, and thereafter ice-cooled, and the precipitate was collected by filtration, washed with water, and then dried to obtain 356 mg of cis-2-hydroxymalonato-1-amino-1-aminomethylcyclohexane platinum.

The resulting compound was suspended in 15 ml of water, and 0.67 ml 1 N sodium hydroxide solution was added to dissolve the compound. The resulting solution was filtered, after which the filtrate was

concentrated and then dried, and 10 ml of acetone was added. The resulting mixture was stirred and then filtered, and the resulting residue was washed with acetone to obtain 288 mg of compound No. 14.

Example 17

cis-bis(Chloroacetato)-1-amino-1-aminomethylcyclohexane platinum (compound No. 15).

A mixture of 394 mg of the platinum complex obtained in Example 5-(1), 333 mg of silver nitrate and 6 ml of water was stirred at room temperature for 4 hours and then filtered, and the precipitate on the filter was washed with water. The filtrate and the washings were combined, followed by adding thereto a solution prepared by dissolving 286 mg of chloroacetic acid in 1 ml of water and neutralizing the resulting solution to pH7 with 30% sodium hydroxide solution. The resulting mixture was stirred at room temperature for 3 hours and then at 60° to 65° for 1 hour. The mixture was then ice-cooled, and the formed precipitate was collected by filtration, washed with water, and then dried to obtain 357 mg of crystals of compound No. 15. The crystals were dissolved in 36 ml of methanol with heating, after which the resulting solution was treated with active carbon, concentrated, ice-cooled and then filtered, and the resulting residue was washed with methanol to obtain 221 mg of white crystals.

Example 18

cis-Bispyruvato-1-amino-1-aminomethylcyclohexane platinum (compound No. 16).

A mixture of 394 mg of the platinum complex obtained in Example 5-(1), 333 mg of silver nitrate and 6 ml of water was stirred at room temperature for 4 hours and then filtered, and the precipitate on the filter was washed with water. The filtrate and the washings were combined and then passed through a column packed with an anion-exchange resin Dowex 1-8X® (OH type, manufactured by Dow Chemical Corp.). To the resulting aqueous solution was added 176 mg of pyruvic acid, and the resulting mixture was allowed to stand overnight. The solution was then concentrated and the residue was dissolved in 10 ml of ethanol, after which the resulting solution was ice-cooled, and the formed precipitate was collected by filtration, washed with ethanol, and then dried to obtain 70 mg of light-yellow crystals of compound No 16.

Example 19

cis-2-Ethylmalonato-1,2-diamino-2-ethylbutane Platinum (compound No. 9).

In 8.5 ml of water was suspended 1.70 g of cis-diiodo-1,2-diamino-2-ethylbutane platinum obtained in Example 2, and 1.00 g of silver nitrate was added, after which the temperature was slowly raised to 50°C, and the mixture was stirred at 50° to 55°C for 30 minutes. After the mixture was cooled to room temperature, the deposited silver iodide was filtered off. To the filtrate obtained was added a solution prepared by dissolving 436 mg of 2-ethylmalonic acid in 1.5 ml of water and neutralizing the resulting solution to pH6. The resulting solution was stirred at 50° to 55°C. Therafter, the solution was treated with active carbon, concentrated to a volume of about 5 ml, and then ice-cooled, after which the deposited crystals were collected by filtration, washed with water, and then dried to obtain 828 mg of white crystals of compound No. 9.

Example 20

cis-2-Hydroxymalonato-1,2-diamino-2-ethylbutane platinum (compound No. 10).

Reaction was conducted in the same manner as in Example 19, except that 380 mg of hydroxymalonic acid was used in place of 2-ethylmalonic acid, to form a white precipitate. After ice-cooling, the formed precipitate was collected by filtration, washed with water, and then dried to obtain 317 mg of crystals of compound No. 10. The filtrate was concentrated to a volume of about 2 ml to about 108 mg of crystals of compound No. 10 additionally. Both the former and the latter crystals were dissolved in 12 ml of water and filtered, and 36 ml of methanol was added to the filtrate, after which the resulting mixture was ice-cooled, and the deposited crystals were collected by filtration, washed with methanol, and then dried to obtain 283 mg of compound No. 10 in a pure form.

Example 21

cis-2-Ethylmalonato-1-amino-1-aminomethylcyclopentane platinum (compound No. 22).

Reaction was conducted in the same manner as in Example 19, except that 1.69 g of cis-diiodo-1-amino-1-aminomethylcyclopentane platinum was used in place of cis-diiodo-1,2-diamino-2-ethylbutane platinum. The reaction mixture was treated with active carbon and then concentrated to a volume of about 10 ml, and 60 ml of acetone was added, after which the resulting mixture was cooled, and the deposited crystals were collected by filtration and washed with acetone to obtain 591 mg of white crystals of compound No. 22.

Example 22

cis-2-Hydroxymalonato-1-amino-1-aminomethyl-cyclopentane platinum (compound No. 23).

Reaction was conducted in the same manner as in Example 20, except that 1.69 g of cis-diiodo-1-amino-1-aminomethylcyclopentane platinum was used in place of cis-diiodo-1,2-diamino-2-ethylbutane platinum. The formed precipitate was collected by filtration after ice-cooling, washed with water, and then dried to obtain 743 mg of light-brown crystals. The crystals were dissolved in 75 ml of water with heating, after which the resulting solution was treated with active carbon, concentrated to a volume of about 15 ml, and then

cooled, and the deposited crystals were collected by filtration, washed with water, and then dried to obtain 592 mg of white crystals of compound No. 22.

Example 23

cis-2-Ethylmalonato-1-amino-1-aminomethylcyclohexane platinum (compound No. 17).

Reaction was carried out in the same manner as in Example 19, except that 1.73 g of cis-diiodo-1-amino-1-aminomethylcyclohexane platinum was used in place of cis-diiodo-1,2-diamino-2-ethylbutane, to form a white precipitate. After cooling, the crystals were collected by filtration, washed with water, and then dried to obtain 645 mg of crystals of compound No. 17. The crystals thus obtained were dissolved in 52 ml of water with heating, and the resulting solution was treated with active carbon, concentrated to a volume of about 15 ml, and then cooled, and the deposited crystals were collected by filtration, washed with water, and then dried to obtain 355 mg of white crystals of compound No. 17.

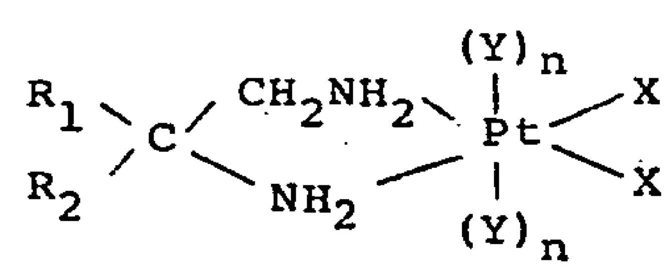
Example 24

cis-Tetrachloro-1-amino-1-aminomethylcyclohexane platinum (compound No. 12)

In 5 ml of water was suspended 400 mg of cis-dichloro-1-amino-1-aminomethylcyclohexane platinum (II), and chlorine gas was bubbled therethrough at 70°C for about 1 hour. Subsequently, the reaction mixture was cooled, and the deposited crystals were collected by filtration, washed with water, and then dried to obtain 250 mg of yellow crystals of compound No. 12.

CLAIMS

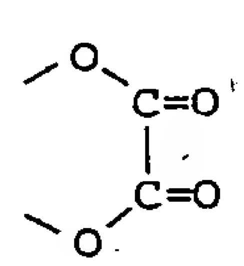
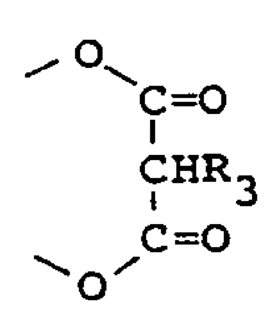
1. A platinum-diamine complex of formula:



wherein R_1 and R_2, which may be identical or different, each represent an alkyl group of 1 to 3 carbon atoms or jointly represent an alkylene group of 3 to 6 carbon atoms; the two X's, which may be identical or different, each represent a halogen, a

$$-\mathrm{O}-\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}-\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}-\mathrm{CH_3} \quad \text{or} \quad -\mathrm{O}\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}\mathrm{CH_2Cl}$$

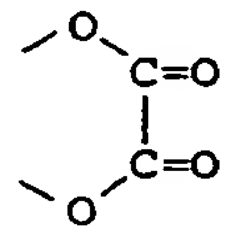
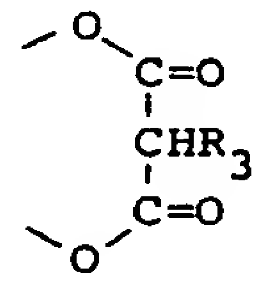
group or jointly represent a

 or 

group in which R_3 is a lower alkyl group or a $-OM$ group, wherein M is an atom or group which can become a monovalent cation; Y is an $-OH$ group or a halogen; and n is 0 or 1, with the proviso that n is 1 when R_1 and R_2 jointly represent an alkylene group of 5 carbon atoms, and X is chlorine.

2. A platinum-diamine complex according to claim 1, wherein R_1 and R_2, which may be identical or different, each represent a methyl or ethyl group or jointly represent an alkylene group of 4 or 5 carbon atoms, and the two X's, which may be identical or different, each represent chlorine, a

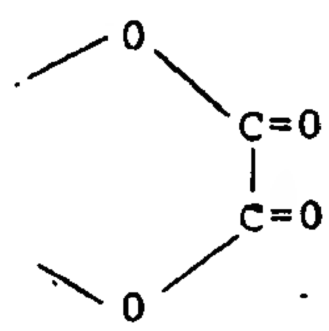
$$-\mathrm{O}-\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}-\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}-\mathrm{CH_3} \quad \text{or} \quad -\mathrm{O}\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}\mathrm{CH_2Cl}$$

group or jointly represent a  or 

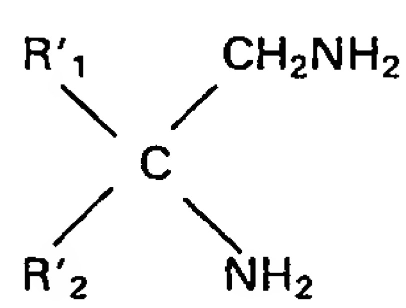
group in which R_3 is a methyl, ethyl, $-OH$ or $-ONa$ group.

3. A platinum-diamine complex according to claim 2, wherein R_1 and R_2, which are the same and represent a methyl group or an ethyl group, respectively, or jointly represent an alkylene group of 4 or 5 carbon atoms; the two X's, which may be identical or different, each represent chlorine or a $-O\underset{\underset{O}{\|}}{C}CH_2Cl$

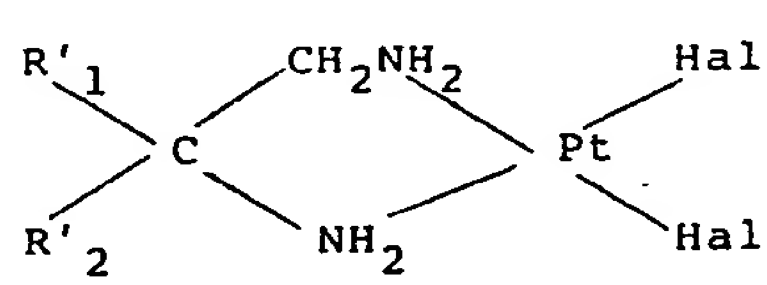
group or jointly represent a

 group; and Y is an $-OH$ group or chlorine.

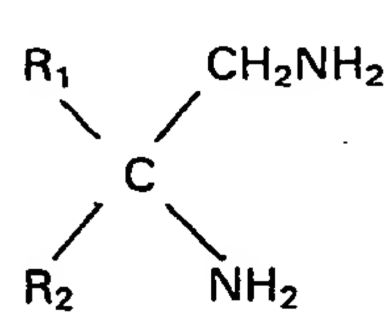
4. A platinum-diamine complex according to claim 1 specifically identified herein.
5. *cis*-Dichloro-1,2-diamino-2-methylpropane platinum.
6. *cis*-Tetrachloro-1,2-diamino-2-methylpropane platinum.
7. *cis*-Dichloro-1,2-diamino-2-ethylbutane platinum.
8. *cis*-Oxalato-1,2-diamino-2-ethylbutane platinum.
9. *cis*-Dichloro-*trans*-dihydroxy-1-amino-1-aminomethylcyclohexane platinum.
10. *cis*-Tetrachloro-1-amino-1-aminomethylcyclohexane platinum.
11. *cis*-Oxalato-1-amino-1-aminomethylcyclohexane platinum.
12. *cis*-Bis(chloroacetato)-1-amino-1-aminomethylcyclohexane platinum.
13. *cis*-Dichloro-1-amino-1-aminomethylcyclopentane platinum.
14. *cis*-Dichloro-*trans*-dihydroxy-1-amino-1-aminomethycylopentane platinum.
15. *cis*-Oxalato-1-amino-1-aminomethylcyclopentane platinum.
16. A process for preparing a platinum-diamine complex according to any one of the preceding claims wherein (a) a compound of formula $M'_2Pt(Hal)_4$ is reacted with a compound of formula:



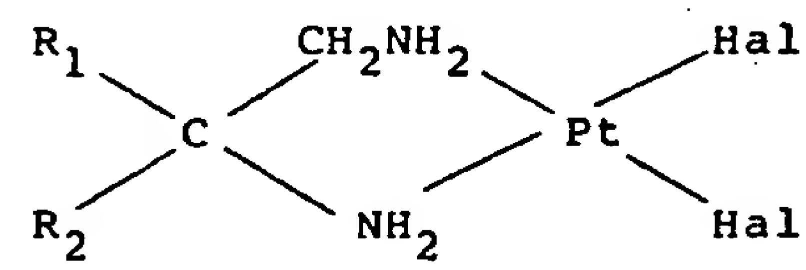
to form a platinum-diamine complex of formula:



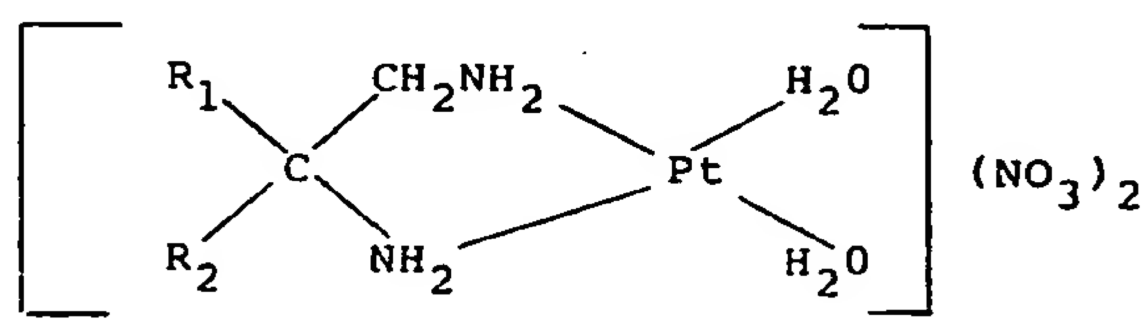
wherein R'_1 and R'_2, which may be identical or different, each represent an alkyl group of 1 to 3 carbon atoms or jointly represent an alkylene group of 3 to 6 carbon atoms; M' is an alkali metal; and Hal is a halogen with the proviso that Hal is not chlorine if R'_1 and R'_2 jointly represent an alkylene group of 5 carbon atoms; or (b) a compound of formula $M'_2Pt(Hal)_4$ is reacted with a compound of formula



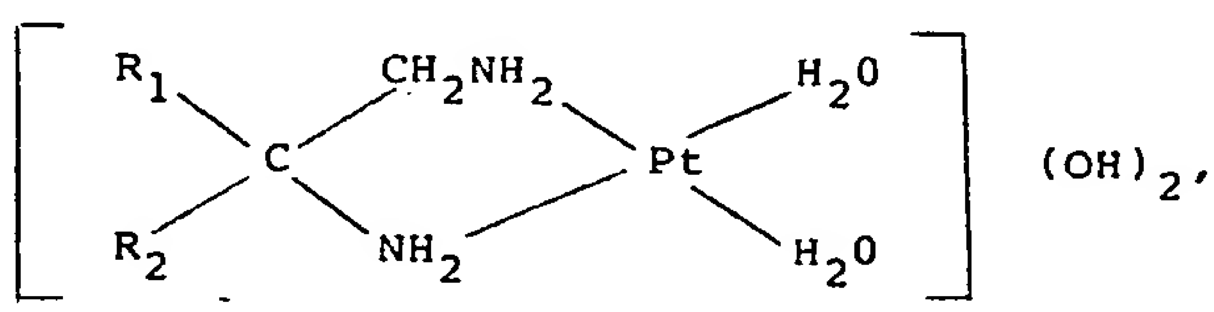
to form a platinum-diamine complex of formula:



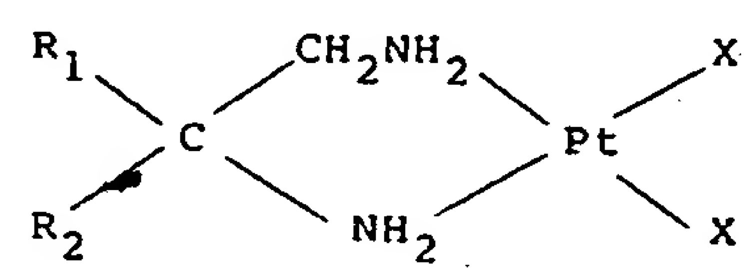
wherein M' and Hal are as defined above and R_1 and R_2 are as defined in claim 1, which is then reacted with an aqueous solution of $AgNO_3$ to form an aqueous solution of an aquo-complex of formula:



which is then either reacted with a compound of formula $(Z)_m-X$, wherein Z is an atom or group which is able to become either a monovalent or a divalent cation, m is 1 or 2 and X is as defined in claim 1, with the proviso that if X is a halogen, Z is not hydrogen, or is treated with a strongly basic ion-exchange resin to form an aqueous solution of a compound of formula:

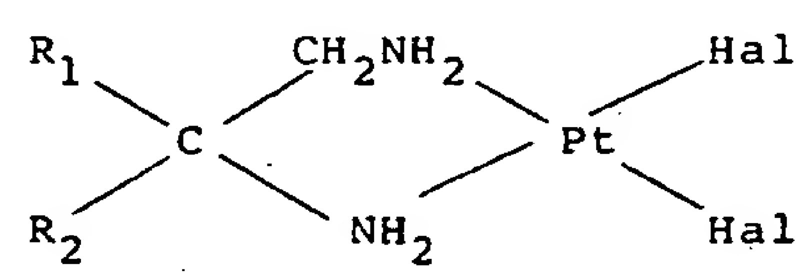


which is then reacted with an acid of formula $(H)_m-X$, wherein m and X are as defined above, to form a platinum-diamine complex of formula:

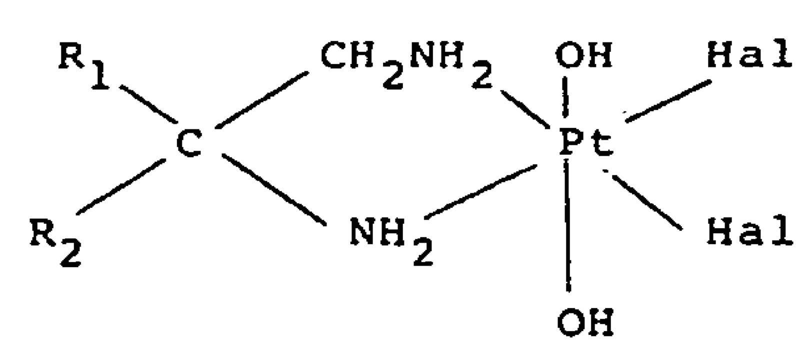


or;

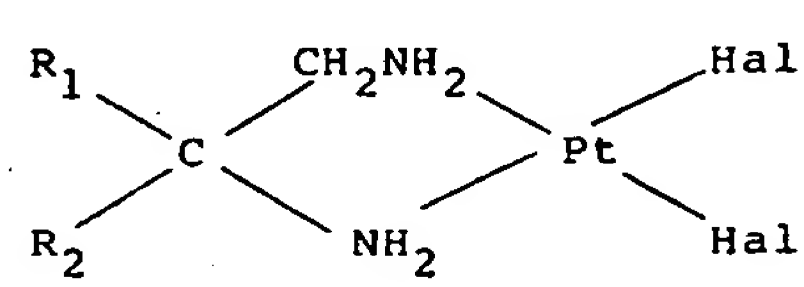
(c) a compound of formula:



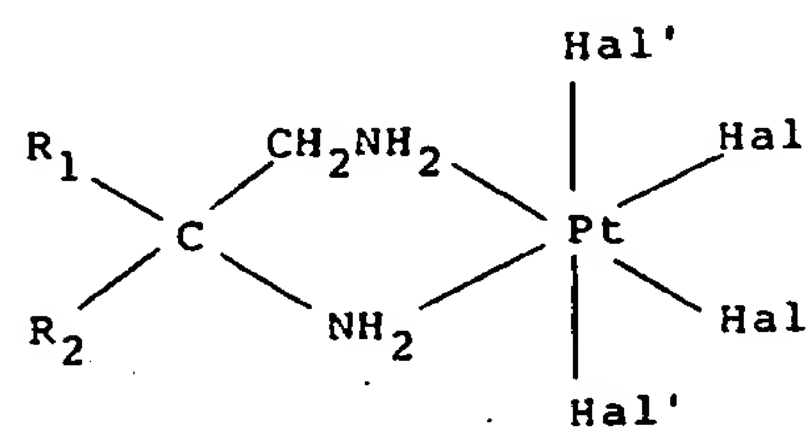
is reacted with a peroxide to form a platinum-diamine complex of formula:



wherein R_1, R_2 and Hal are as defined above, which is then optionally reacted with a hydrogen halide of formula HHal', or the compound of formula:



is reacted with a halogen to form a platinum-diamine complex of formula:



wherein the Hal' groups, which may be identical or different each represent a halide.

17. A process according to claim 16 substantially as herein described with reference to any one of the Examples.

18. A compound according to any one of claims 1 to 15 for use in a method of treatment of the human or animal body.

19. A compound according to any one of claims 1 to 15 for use in the treatment of a tumour in the human or animal body.

Printed in the UK for HMSO, D8818935, 4/85, 7102.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.